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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,440	03/30/2001	Lucio Miele	4239-58051	1318

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KLARQUIST SPARKMAN, LLP
121 S.W. SALMON STREET, SUITE #1600
ONE WORLD TRADE CENTER
PORTLAND, OR 97204-2988

EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	09/806,440	MIELE ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,8-13,16-18,22,23,30-32,72-75 and 83-88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *88* is/are allowed.

6)☒ Claim(s) *1,2,5,8-13,16-18,22,23,30-32,72-75 and 83-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-2, 5, 8-13, 16-18, 22-23, 30-32, 72-75, and 83-88 are pending in the instant application.

Summary of Telephone Interview

2. It is noted that Applicant's did not mention that Applicants proposed the filing of a Rule § 1.132 Declaration in order to address the pending rejection under 35 USC § 112, for lack of enablement. The examiner also stated that declaration evidence would have to be commensurate in scope to the claimed invention, and the disclosure as originally filed.

Response to Arguments

Claim Rejections - 35 USC § 112

3. Claims 1-2, 5, 8-13, 17-18, 22-23, 30-32, 72-75 and 80-86 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description), for the reasons of record set forth in the Official Action mailed 12-18-03.

Applicant's arguments filed 4-19-04 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by way of amending the instant claims to recite "human Notch-1," and by providing references to support their assertion that the genus of agents that interfere with human Notch-1 expression or function was known in the prior art. However, contrary to Applicant's assertions, although Applicants have amended the instant claims to recite "human Notch-1," this amendment does not provide a structural description of "human Notch-1," or the full scope of agents that inhibit the expression or function of human

Notch-1. Absent evidence to the contrary, the limitation "human Notch-1" still encompasses allelic variants, splice variants, and sequences that have a recited degree of identity (similarity, homology), which still encode a "human Notch-1" gene. Moreover, none of the references cited by Applicants to support their arguments provide agents that *specifically* inhibit the expression or function of "human Notch-1." The specification as filed describes antisense oligonucleotides according to SEQ ID NO: 6, 8 and 11, which target human Notch-1 of GenBank Accession No. M73980, and antibodies targeting a recombinant antigen comprising the EGF repeats 11 and 12 of human Notch-1 (also set forth in M73980). However, the instant claims are drawn to a broad class of antisense oligonucleotides that interfere with the expression of gene sequences of allelic variants, splice variants, and sequences that have a recited degree of identity (similarity, homology), and which encode a "human Notch-1" gene other than that disclosed in GenBank Accession No. M73980. There is no evidence that the antisense oligonucleotides or antibody described by Applicants can be used to predict the full scope of agents that are encompassed by the instant claims. Additionally, the instant claims are broadly drawn to antagonizing agents, including antibodies that target all allelic and polymorphic forms of the human Notch-1 protein and gene sequence. It is unclear how antibodies which target only a specific region of the human Notch-1 protein, can be used to demonstrate possession of the full scope of antibodies that may target other portion of the human Notch-1 protein according to GenBank M73980 or other forms of human Notch-1 protein. The specification as filed provides insufficient written description to support the genus of agents, which interfere with the function of human Notch-1 protein or expression of human Notch-1 gene sequence, encompassed by the instantly claimed invention.

Therefore, only the antisense oligonucleotides according to SEQ ID NO: 6, 8, and 11 and the antibody targeting the recombinant antigen rh11-12 of human Notch-1 (M73980), but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant.

4. Claims 1-2, 5, 8-13, 16, 30-31, 72-75, and 84-87 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for practicing the claimed methods in vitro comprising the administration of antisense agents that interfere with Notch expression, does not reasonably provide enablement for practicing the claimed methods in vivo comprising the administration of antisense oligonucleotide agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record set forth in the Office Action mailed 12-18-03.

5. Applicant's arguments filed 4-19-04 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that because the specification as filed provides tissue culture data wherein Applicants have demonstrated that several Notch-1 antisense and several Notch-1 antibodies, in combination with a differentiation agent, induce apoptosis, this decreases the unpredictability in this art. Moreover, Applicants argue that one skilled in the art would expect similar results *in vivo*. Additionally, Applicants cite MPEP § 2100 to assert that the Federal Circuit has held that *in vitro* results can be sufficient to show pharmacological activity. Additionally, Applicants cite *Cross v. Iizuka* 753 F.2d 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985 and *In re Brana,* 51 F.3d 1560, 34 USPQ2d 1436 (Fed.

Cir. 1995) to support their assertion that *in vitro* results can be sufficient to show pharmacological activity. However, it is noted that neither of the cited cases reflect the unique case of the unpredictability associated with the use of antisense oligonucleotides *in vivo* for the treatment of diseases as set forth in the instant application. Moreover, Applicants do not address the decision by the Federal Circuit described in MPEP § 2164.06(b), in particular In Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 52 USPQ2d 1129 (Fed. Cir. 1999), the court held that claims in two patents directed to genetic antisense technology (which aims to control gene expression in a particular organism), were invalid because the breadth of enablement was not commensurate in scope with the claims. Both specifications disclosed applying antisense technology in regulating three genes in E. coli. Despite the limited disclosures, the specifications asserted that the "[t]he practices of this invention are generally applicable with respect to any organism containing genetic material which is capable of being expressed ... such as bacteria, yeast, and other cellular organisms." The claims of the patents encompassed application of antisense methodology in a broad range of organisms. Ultimately, the court relied on the fact that (1) the amount of direction presented and the number of working examples provided in the specification were very narrow compared to the wide breadth of the claims at issue, (2) antisense gene technology was highly unpredictable, and (3) the amount of experimentation required to adapt the practice of creating antisense DNA from E. coli to other types of cells was quite high, especially in light of the record, which included notable examples of the inventor's own failures to control the expression of other genes in E. coli and other types of cells. Thus, the teachings set forth in the specification provided no more than a "plan" or "invitation" for those of skill in the art to experiment using the technology in other types of cells."

In the same manner, Applicants provide cell culture data and assert that their disclosure is sufficient such that the skilled artisan may practice the claimed methods for treatment purposes in a human for the treatment of a variety of disorders. Applicants cell culture experiments provide no guidance for administering the claimed agents to an individual such that said agents can interfere with the expression of Notch in a target cell, and wherein apoptosis is induced in said target cell, and further produce treatment effects in said individual for cancers such as cervical cancer, breast cancer, colon cancer, melanoma, seminoma, lung cancer, and hematopoietic malignancy. There is no specific guidance provided in the specification as filed, or generally known in the art for the concurrent delivery of a differentiation agent and an agent that inhibits human Notch-1 function or expression, for amelioration or treatment of any particular disease.

According to Applicants, their *in vitro* data reduces the unpredictability in the art. There are multiple aspects of unpredictability associated with antisense, in particular, as described by Branch (1998) in the prior Office Action, "their unpredictability confounds research applications of nucleic acid reagents." "[N]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,..."; "Because knowledge of their underlying mechanism is typically."..[unknown], "non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always need to establish a compound's primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is

true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its does-response curve and therapeutic index is known."; [c]ompared to the does response curves of conventional drugs, which typically span two to three orders of magnitude, those antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible in vivo, effective antisense molecules must be determined empirically by screening lager numbers of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most sites. [s]ince accessibiltiy cannot be predicted, rational design of antisense molecules is not possible."' and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition in vivo is beginning to be explored...**[i]t is not yet clear whether in vitro screening techniques...will identify ODNs that are effective in vivo.**" However, Applicants make no attempt to address which aspects of unpredictability the *in vitro* experiments set forth in the specification as filed, are able to overcome.

Additionally, it is clear from Jen et al. (as described in the prior Office Action) that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome. One in the art would be required to perform undue trial and error experimentation to practice the claimed invention. The quantity of experimentation would include the determination of specific antisense sequences that would be effective in vivo and how to deliver sufficient antisense to target cells of a disease contemplated for Notch antisense therapy, for example.

Conclusion

6. Claim 88 is free of the prior art.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Janet L. Epps-Ford, Ph.D.
Patent Examiner
Art Unit 1635

JLE